REMARKS

Status of the Claims

Claims 20, 21, and 83-149 were pending in the present application. Claims 93-94, 108, 124-126, and 139 were withdrawn from consideration and remaining claims were rejected. By virtue of this response, claims 88-96 and 119-127 have been cancelled, claims 20, 21, 97, 98, 100-104, 106-109, 111, 128, 129, 131-135, 137-140, 142, 148, and 149 have been amended, and no new claims have been added. Accordingly, claims 20, 21, 83-87, 97-107, 109-118, 128-138, and 140-149 are currently under consideration.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation, continuation-in-part, and/or divisional applications.

Amendments to the Specification

The "Drawings" section in the specification has been amended to more closely correspond to the labeling of the Figures as requested by the Examiner. No new matter is added.

Amendments to the Claims

Claims 88-96 and 119-127 have been cancelled, claims 20, 21, 97, 98, 100-104, 106-109, 111, 128, 129, 131-135, 137-140, 142, 148, and 149 have been amended, and no new claims have been added. No new matter has been added.

Independent claims 20 and 21 have been amended to replace "free-living microbe" and "microbe" with "modified bacterium." Amendments to replace "microbe" with "bacterium" have also been made in dependent claims 97, 100-103, 109, 111, 128, 131, 133, 134, 140, and 142 for consistency with the independent claims. Support for these amendments are found throughout the application as filed, including, e.g., in lines 17-18 of paragraph [0006] at page 4, in lines 26-29 of

paragraph [0079] at page 30, and in lines 1-15 of paragraph [0091] at page 37. Claims 97, 100-102, 128, 131-133, 148, and 149 have been amended to refer directly to claim 20 or 21 in light of the amendment of claims 20 and 21 and cancellation of claims 96 and 127 by virtue of this Amendment.

Claims 20 and 21 have both been amended to explicitly state that the bacterium is attenuated for proliferation relative to the bacterium prior to modification. Support for this amendment is found, e.g., in lines 1-9 and lines 20-26 of paragraph [0089] at pages 34-35.

Claim 20 has further been amended to explicitly state that the gene expression in the modified bacterium is active. Support for this amendment is found, e.g., in lines 1-3 of paragraph [0005] at page 3, in paragraph [0078] at page 29, in lines 1-9 and 42-45 of paragraph [0079] at pages 29-30, in lines 48-49 of paragraph [0089] at page 35, in paragraph [0091] at page 37, in lines 1-5 of paragraph [0256], and in paragraph [0093] at pages 38-39.

Claims 97, 103, 128, 134 have been amended to explicitly state that the attenuation of the ability of the bacterium to repair its nucleic acid is "relative to wild type." Support for these amendments is found, e.g., in paragraph [0118] at pages 55-56.

Similarly, claims 98, 104, 129, and 135 have been amended to explicitly state that the bacterium is defective with respect to a DNA repair enzyme "relative to wild type." Support for these amendments is found, e.g., in paragraph [0118] at pages 55-56. Claims 98, 104, 129, and 135 are further amended to explicitly state that the bacterium is defective with respect to a DNA repair enzyme due to the genetic mutation. Support for these amendments is found, e.g., in paragraphs [0114] to [0115] at pages 52-54, and in paragraphs [0117]-[0120] at pages 55-57.

Minor, clarifying amendments are also made to claims 103, 106, 107, 111, 128, 137, 138, and 142. No new matter is added.

Claims 108 and 139 have been amended to explicitly state that the "the mutation in the *actA* gene attenuates the ability of the *Listeria* to spread relative to wild type and the mutation in the *inlB* gene attenuates the ability of the *Listeria* to invade at least some cells relative to wild type."

Support for these amendments is found, e.g., in paragraph [0113] at pages 50-51 and in paragraph [0016] at pages 54-55.

Objection to the Specification

The Examiner has objected to the specification because the "Drawings" section allegedly did not properly correspond to the figures. By virtue of this Amendment, the section entitled "Drawings" in the specification has been amended to more closely correspond to the labeling of the Figures as requested by the Examiner. Accordingly, Applicants respectfully request that the objection to the specification be withdrawn.

Claim Objections

The Examiner has objected to claims 99, 105, 121, 130, and 136 because the claims contain non-elected subject matter. The Examiner has required that the claims be amended to remove non-elected subject matter.

In response, Applicants respectfully submit that no amendment of claims 99, 105, 130, and 136 to remove non-elected subject matter should be required at this time. These claims are generic claims, and the previous election of a mutation in *uvrA* and *uvrB* by Applicants in response to the Office Action mailed October 3, 2006, was a *species* election only.

As indicated in MPEP §821.02, "Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141." Thus, if a generic claim is found to be allowable, Applicants request consideration of an additional reasonable number of species not previously elected. If no generic claim is found to be allowable, but claims readable upon the elected species are found to be allowable with respect to the elected species, removal of non-elected species from the claims may be proper (see, e.g., MPEP 821.02). Since no final determination as to the allowability of the claims has been made in this application, removal of any non-elected species from claims 99, 105, 130, and 136 at this time would be premature.

Claim 121 has been cancelled by virtue of this Amendment, and, thus, the objection to this claim is rendered moot.

Accordingly, Applicants respectfully request that the objection to claims 99, 105, 130, and 136 as containing non-elected subject matter be withdrawn.

Provisional Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 20-21, 83-92, 94-99, 100-105, 106, 107, 109-121, 122-130, 131-136, 137-138 and 139-149 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32, 33, 60, 66, 90, 94, 101 and 103 of copending Application No. 11/173,770. In response, Applicants note that this is a provisional rejection only. Applicants will address this rejection, if maintained, at the appropriate time if conflicting claims are found allowable.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 20-21, 83-92, 94-99, 100-105, 106, 107, 109-121, 122-130, 131-136, 137-138 and 139-149 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse this rejection. Since claims 88-92, 94-96, and 119-127 are cancelled by virtue of this Amendment, the rejection of these claims is considered moot.

1. Claims 20 and 21 were found to be vague and confusing because it was allegedly unclear what was meant and encompassed by the term "free-living microbe." Applicants respectfully traverse this rejection.

Applicants contend that the Examiner's characterization of "free-living microbe" is incorrect, and note that the specification clearly indicates that the term"free-living microbes" does not encompass viruses. See, e.g., lines 9-11 of paragraph [0079] at page 29. Nevertheless, in the

interest of expediting prosecution, and without acquiescing as to the merits of the rejection, the claims have now been amended to refer to a "bacterium" rather than a "free-living microbe."

2. Claims 20 and 21 were also found to be "vague and confusing because the structure/source/identification of the microbe" was allegedly unclear. The Examiner states that the claims provide a "mere recitation of vague process with an unspecified compound." The Examiner further states that the 'type of microbe and the type/location of mutation" should be included in the claim. Applicants respectfully traverse this rejection.

Applicants contend that claims 20 and 21 would be neither vague nor confusing to one of ordinary skill in the art. One of ordinary skill in the art would readily be able to determine if a certain bacterium was a bacterium "wherein the nucleic acid of the bacterium had been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the bacterium is attenuated for proliferation relative to the bacterium prior to modification." Attenuation of the bacteria for proliferation following treatment with a particular nucleic acid targeted compound can readily be assessed using methods routine to those of ordinary skill in the art. Examples of assays useful in this regard are provided in Applicants' specification at page 34-36 and in Example 1 (especially paragraph [0156] at pages 76-77). As taught in Applicants' specification, the level of attenuation with a particular compound can often be adjusted by varying the dosage of the nucleic acid targeted compound. Applicants contend that it is not necessary to know the exact location of a modification of the bacterial genome, such as a crosslink formed by a psoralen upon irradiation with UVA, in a bacterium to determine the metes and bounds of the claims.

Applicants further contend that there is nothing vague or confusing about the "nucleic acid targeted compound that reacts directly with the nucleic acid" term recited in the claims. Lines 22-24 of paragraph [0097] of the specification note, "A nucleic acid targeted compound is any compound that has a tendency to preferentially bind nucleic acid, i.e. has a measurable affinity for nucleic acid." Further, lines 6-12 of paragraph [0096] at pages 39-40 of the specification indicate that not all nucleic acid targeted compounds react "directly with the nucleic acid (i.e., all or some portion of the compound covalently binds to the nucleic acid)." A variety of such types of nucleic

acid targeted compounds are known in the art and identified in Applicants' specification, e.g., in paragraphs [0098]-[0100] at pages 41-44 of the specification.

3. Claim 21 was found to be vague and indefinite because it was allegedly unclear whether the "antigen" was a heterologous antigen or one already expressed by the microbe. Applicants respectfully traverse this rejection.

Applicants contend that, contrary to the Examiner's assertions, the use of the term "antigen" in claim 21 is clear. Since no language in claim 21 explicitly limits the term "antigen" to either "a heterologous antigen" or "one already expressed by the microbe," the term "antigen" encompasses both of these types of antigens. Support for this is found in the specification, e.g., at lines 7-9 of paragraph [0062] at page 24.

4. Claims 90-92, 99, 105, 106, 107, 121, 122, 123, 130, 136, 137, and 138 were found to be vague and indefinite because it was allegedly unclear whether "the mutations are the reason for the attenuated proliferation or if they are in addition to the attenuated proliferation" and it was allegedly unclear "what is encompassed by the mutation, does it result in the disclosed gene unable to function, just cause reduced function, etc." See page 6 of the Office Action mailed January 26, 2007.

By virtue of this Amendment claims 90-92 and 121-123 are cancelled. The rejections with respect to these claims are therefore considered moot. Applicants respectfully traverse this rejection with respect to the remaining rejected claims.

Applicants contend that claims 99, 105, 106, 107, 130, 136, 137, and 138 are neither vague nor indefinite. Applicants contend that it would be clear to one of ordinary skill in the art from the claim language that the genetic mutations in *phr*B, *uvr*A, *uvr*B, *uvr*C, *uvr*D and/or *rec*A have the effect of causing the bacterium to be defective with respect to a DNA repair enzyme, thereby attenuating the ability of the bacterium to repair its nucleic acid that has been modified. The modification of the bacterium by reaction with a nucleic acid targeted compound to attenuate its proliferation, however, may be more indirectly affected by the genetic mutations in *phr*B, *uvr*A,

*uvr*B, *uvr*C, *uvr*D and/or *rec*A. For instance, in some embodiments, a bacterium comprising the mutations will advantageously have a higher sensitivity to the modification than wild type. See, e.g., paragraphs [0114]-[0115] at pages 52-54 of the specification. Applicants further contend that it would be clear to one of ordinary skill in the art that the genetic mutations in *phr*B, *uvr*A, *uvr*B, *uvr*C, *uvr*D and/or *rec*A need not necessarily completely eliminate the function of the gene product. See, e.g., paragraph [0118] at pages 55-56.

In view of the foregoing, Applicants respectfully request that the rejection of claims 20-21, 83-87, 97-99, 100-105, 106, 107, 109-118, 128-130, 131-136, 137-138 and 139-149 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims Rejections under 35 U.S.C. § 112 – Scope of Enablement

Claims 20-21, 83-92, 94-99, 100-105, 106, 107, 109-121, 122-130, 131-136, 137-138, and 139-149 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner stated that the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims."

Applicants respectfully traverse this rejection. Since claims 20-21, 83-87, 97-99, 100-105, 106, 107, 109-118, 128-130, 131-136, 137-138 and 139-149 are cancelled by virtue of this Amendment, the rejection of those claims is moot.

The basis for the Examiner's enablement rejection appears to be essentially three-fold:

1. The claims are allegedly not enabled for any free-living microbe.

2. The claims are allegedly not enabled for any nucleic acid targeted compound.

3. The claims are allegedly not enabled for any mutation in *uvrA* and/or *uvrB*.

Applicants disagree and address each of these assertions in turn below.

1. The full scope of the claims for any free-living microbe, including any bacterium, is enabled.

Applicants contend that the full scope of the original claims reciting "free-living microbe" are fully enabled. Applicants note that the term "free-living microbe" does not include viruses. See, e.g., lines 9-11 of paragraph [0079] at page 29 of the specification. Nevertheless in order to expedite prosecution, and without acquiescing as to the merits of the rejection, claims 20 and 21 and the dependent claims have now been amended to recite "bacterium" instead of "free-living microbe."

Applicants contend that the full scope of the claims, as amended, are fully enabled. In addition to the extensive guidance and examples provided for *Listeria monoctyogenes* (which do not seem to have been questioned by the Examiner), Applicants' specification provides a working example of the attenuation of proliferation of *Escherichia coli* and *Escherichia coli uvrABC* mutants in Figure 3 and Example 3 (paragraphs [0160]-[0161] at pages 80-82). In addition, Applicants provide guidance regarding the treatment of *Bacillus anthracis* in, e.g., Example 9 (paragraphs [0190]-[0199] at pages 100-103) and in the working example of the attenuation of proliferation of *Bacillus anthracis* in Example 21 (paragraphs [0240]-[0249] at pages 129-133) of the specification. Thus, contrary to the assertions of the Examiner, experimental results are provided for bacteria other than *Listeria monocytogenes*, including *B. anthracis* mutants. Further guidance regarding *B. anthracis*, including the production of asporagenic mutants, is provided, e.g, in Examples 37-44 (paragraphs [0290]-[0308] at pages 151-162) of the specification.

Furthermore, Applicants note that the methods of attenuating bacteria for proliferation by modifying the nucleic acid of the bacteria with a nucleic acid targeted compound that reacts directly with the nucleic acid that are disclosed in the specification are often largely or wholly independent of the particular sequence of the genomic nucleic acid. See, e.g., the extensive disclosure of a variety of exemplary nucleic acid targeted compounds in paragraphs [0098] – [0100] at pages 41-44, the majority of which one of ordinary skill in the art would not view as being sequence specific in the manner in which they modify nucleic nucleic acids. For this reason, the modification method

is generally applicable to a wide range of bacteria, regardless of species or genus. For instance, modification with a psoralen (S59) and UVA had previously been shown to be effective at inactivating a wide variety of bacteria. See, e.g., Lin (1998) Science and Medicine 5:2 11 (cited in paragraph [0296] of the specification) which reports that the S-59 psoralen and UVA treatment reduces the infectivity of a number of different types of bacteria, such as *Staphylococcus epidermidis*, *Staph. Aureus*, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Corynebacterium minutissimum*, *Escherichia coli*, *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Salmonella choleraesuis*, *Yersinia enterocoliticus*, and *Pseudomonas aeruginosa*.

In addition, Applicants contend that assays are disclosed in Applicants' specification and/or are known to those of ordinary skill in the art that allow for identification/selection of attenuated bacteria suitable for use in the claimed methods without undue experimentation. Examples of assays useful in this regard are provided in Applicants' specification at page 34-36 and in Example 1 (especially paragraph [0156] at pages 76-77).

With respect to *uvrA* and *uvrB* mutants of bacteria, Applicants first note that many of the claims do not require the presence of a *uvrA* and/or *uvrB* mutation. Claims 20 and 21, for instance, do not require any mutation of the sequence of the genome of the bacteria.

Applicants own specification provide a representative number of *uvrA* and *uvrB* genes and/or *uvrA* and *uvrB* mutants of different types of bacteria. Applicants' specification provides a working example of the attenuation of proliferation of *Escherichia coli uvrA* mutants in Figure 3 and Example 3 (paragraphs [0160]-[0161]. In addition, Applicants provide information regarding *uvrA* and/or *uvrC* genes, e.g., in paragraph [0120] at pages 56-57, in Example 9 (paragraphs [0190]-[0199] at pages 100-103, and in the working example of the attenuation of proliferation of *Bacillus anthracis* in Example 21 (paragraphs [0240]-[0249] at pages 129-133) of the specification. Paragraph [0197] of Applicants' specification also provides information on the sequences of *uvrA* and *uvrB* of another species of bacteria, *Bacillus subtilis*.

Applicants further contend that *uvrA* and *uvrB* genes had been identified in the art for a variety of other types of bacteria at the time of filing. See, e.g., Aravind et al., Nucleic Acids

Research 27(5):1223-1242 (1999), cited in paragraph [0114] at page 52 of Applicants' specification, which states at page 1236, first column, third full paragraph, "The UvrABC excisionase, together with the UvrD helicase that is functionally coupled to it, are the principal components of NER in bacteria (4) and are encoded in all bacterial genomes sequenced to date, including the minimal genomes of *Mycoplasma*." *UvrA* and *uvrB* genes that were known to those of ordinary skill in the art at the time of filing include, for example, *E. coli* (see, e.g., Husain, et al. The Journal of Biological Chemistry, 261:4895-4901 (1986); Arikan et al., Nucleic Acids Research, 14:2637-2650 (1986)), *Salmonella enterica serovar Typhi* (see, e.g., Genbank Acc. No. NC_004631), and *Shigella flexneri* (see, e.g., Genbank Acc. No. AE005674). Since, as stated in § MPEP 2164.01, a "patent need not teach, and preferably omits, what is well known in the art," Applicants contend that in light of the knowledge of those of ordinary skill in the art, *uvrA* and *uvrB* mutant for a variety of bacteria, including *E. coli*, *Salmonella,* and *Shigella* were fully enabled.

2. *The full scope of the claims for any nucleic acid targeted compound that reacts directly with the nucleic acid so that the bacterium is attenuated for proliferation is enabled.*

The Examiner states on page 8 of the Office Action mailed January 26, 2007, with respect to the rejected claims, "The use of any 'nucleic acid targeted compound' is also included which can attenuate proliferation by any means." Applicants respectfully disagree.

Both of the two independent claims, claim 20 and claim 21, specifically recite that the "nucleic acid of the bacterium has been modified by reaction with a *nucleic acid targeted* compound that reacts *directly* with the nucleic acid *so that the bacterium is attenuated for proliferation.*" Lines 22-24 of paragraph [0097] of the specification note, "A nucleic acid targeted compound is any compound that has a tendency to preferentially bind nucleic acid, i.e. has a measurable affinity for nucleic acid." Further, lines 6-12 of paragraph [0096] at pages 39-40 of the specification indicate that not all nucleic acid targeted compounds react "directly with the nucleic acid (i.e., all or some portion of the compound covalently binds to the nucleic acid)."

The Examiner further states the following on page 10 of the Office Action mailed January 26, 2007:

> The instant [*sic*] fails to demonstrate that any compounds, other than psoralen, would result in an attenuated bacterium which would result in a non-virulent/toxic bacterium which would maintain its metabolic activity and still be able to synthesize and create new protein in a sufficient amount. Experimental results are only shown with respect to psoralen and it would take one of skill in the art undue experimentation to discover and test other nucleic acid targeting compounds and the efficacy of the resultant vaccines.

Applicants again respectfully disagree.

Contrary to the Examiner's assertion, Applicants have provided experimental results for a nucleic acid targeted compound other than psoralen. Example 2 of Applicants' specification (paragraph [0159] at page 79, Table 3 at page 80, and Figures 2A and 2B) provides a description of the treatment of *Listeria* strains with a DNA-targeted alkylator β-alanine, N-(acridin-9-yl), 2-[bis(2-chloroethyl)amino]ethyl ester. Results are presented in Example 2 showing that the treated bacteria were attenuated for proliferation and expressed the OVA antigen (Table 2, Figures 2A and 2B).

In addition, Applicants have provided extensive disclosures in the specification regarding a wide variety of nucleic acid targeted compounds. See, e.g., paragraphs [0098] to [0100] at pages 41 to 44 of Applicants specification. Additional information regarding nucleic acid targeted compounds and their reaction with microbial nucleic acids is known in the art. See, e.g., U.S. Patent No. 6,143,490 and 6,093,725, both of which are incorporated by reference in Applicants' specification at the end of paragraph [0099] at page 43.

Attenuation of the bacteria for proliferation following treatment with a particular nucleic acid targeted compound can readily be assessed using methods routine to those of ordinary skill in the art. Examples of assays useful in this regard are provided in Applicants' specification at page 34-36 and in Example 1 (especially paragraph [0156] at pages 76-77). As taught in Applicants' specification, the level of attenuation with a particular compound can often be adjusted by varying

the dosage of the nucleic acid targeted compound. The level of expression of proteins in the treated bacteria can likewise be assayed using methods well known to those of ordinary skill in the art. See, e.g., paragraphs [0092] to [0093] at pages 37-38 of the specification, as well as Example 1 (esp. paragraph [0157] at pages 77-78) and Example 12 (esp. paragraph [0205] at pages 108-109). *In vitro* and *vivo* assays for testing the immunogenicity and/or efficacy of candidate vaccines are known in the art and examples are described, e.g., in paragraphs [0125] to [0126] at pages 60-62, as well as in Examples 4, 5, 6, 14, 15, and 16 of the specification.

3. The full scope of the claims for any mutation in uvrA and uvrB is enabled.

The Examiner has stated on page 10 of the Office Action mailed January 26, 2007, "Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have." Later, at page 11 of the Office Action, the Examiner states, "The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of uvrA and uvrB to target for modifications, in order to produce an attenuated bacterium with the desired phenotype." Applicants, however, contend that adequate direction and guidance *is* provided in Applicants' specification to enable one of ordinary skill in the art to make and/or use the full scope of the claimed invention, including a wide, representative variety of *uvrA* and *uvrB* mutations.

The enablement requirement of 35 U.S.C. § 112, paragraph 1, requires that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands,* 858 F. 2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Furthermore, as stated in MPEP §2164.01, "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir.

1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)."

Applicants respectfully submit that the specification, in light of the knowledge of those of ordinary skill in the art at the time, provides a more than adequate disclosure to enable one of ordinary skill in the art to make and use a wide range of *uvrA* and *uvrB* mutants.

Bacteria may be attenuated for the ability to repair nucleic acid by various routes that are readily attainable by one of ordinary skill in the art without any undue experimentation. It is significant that if a *uvrA* or *uvrB* mutant is generated such that the bacteria are attenuated for repair of nucleic acid, the expression and/or activity of the gene product is being *disrupted* by the mutation(s). Although it may be more of a challenge to identify mutant forms of a protein that maintain function or have improved function, that is not what is required here. Generating functional mutants of a protein can be difficult precisely because it is so easy to render a protein nonfunctional once the sequence is known, even if structural information about the protein is not known. For instance, a frame-shift mutation is going to disrupt any protein's function, regardless of whether or not the structure-function relationship of the protein is known. Likewise, it is generally routine for one skilled in the art to eliminate expression of the protein once the gene sequence has been identified. One of ordinary skill in the art would be readily able to generate, for example, mutants in which a significant part or all of the *uvrA* gene was deleted, mutants in which a stop codon had been placed early in the *uvrA* coding sequence, or mutants in which a insertion mutation causes a frame shift in the UvrA coding sequence. Even many of the possible point mutations that could be generated would be expected to disrupt the production of UvrA and/or UvrB, regardless of the specifics of the structure of these proteins. With respect to point mutations, Griffiths et al. states that, "it is always true that such mutations are more likely to reduce or eliminate gene function (thus they are loss-of-function mutations) than to enhance it. The reason is simple: it is much easier to break a machine than to alter the way that it works by randomly changing or removing one of its components." (page 315; Griffiths, et al. (2002) Modern Genetic Analysis, W.H. Freeman and Co., New York, NY).

Although *uvrA* and *uvrB* genes in different species or genuses of bacteria will generally be expected to differ somewhat in sequence from those genes in *L. monocytogenes*, this doesn't change the fact that disrupting the expression or functionality of the protein in the different species or genus will likewise be routine. If the gene has been identified, its expression or sequence can generally be readily disrupted by one of ordinary skill in the art regardless of how much information is known about the details of the protein.

Applicants respectfully submit that in light of Applicants' teachings and the knowledge of those of ordinary skill in the art, it would be routine for one of ordinary skill in the art to follow the guidelines set out in Applicants' specification to generate a variety of appropriate *uvrA and uvrB* mutants in *Listeria* and other bacteria.

In light of the foregoing remarks, Applicants respectfully request that the rejection of claims 20-21, 83-87, 97-99, 100-105, 106, 107, 109-118, 128-130, 131-136, 137-138 and 139-149 under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement be withdrawn.

Claim Rejections under 35 U.S.C. § 112 – Written Description

Claims 20-21, 83-92, 94-99, 100-105, 106, 107, 109-121, 122-130, 131-136, 137-138 and 139-149 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants respectfully traverse this rejection. Since claims 20-21, 83-87, 97-99, 100-105, 106, 107, 109-118, 128-130, 131-136, 137-138 and 139-149 are cancelled by virtue of this Amendment, the rejection of those claims is moot.

The basis for the Examiner's written description rejection appears to be two-fold:

1. The specification allegedly does not provide adequate written description to support species homologs to the *L. monocytogenes* mutants.

2. The specification allegedly does not provide adequate written description to support the full scope of mutations claimed.

Applicants respectfully traverse this rejection and address both of the above-listed assertions in turn below.

1. The application provides adequate written description to support species homologs to the L. monocytogenes mutants.

As support for her assertion that the specification does not provide adequate written description to support species homologs to *L. monocytogenes* mutants, the Examiner asserts that the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description requirement, citing *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991) and *Regents of the Univ. of Cal. v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), and that the Federal Circuit case law supports her position regarding Applicants' claims.

Applicants respectfully disagree and contend that the Examiner has misapplied the law to Applicants' claims.

It is well established that to meet the written description requirement, an applicant's specification must "convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Marhurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). This is the standard that the Federal Circuit has set. The portions of both of the opinions, *Amgen* and *Eli Lilly*, that were cited by the Examiner concerned claims directed to polynucleotides where the sequences of a representative number of the claimed polynucleotides were not previously known in the art. In a subsequent Federal Circuit opinion, *Falkner v. Inglis*, which concerned claims directed to vaccines comprising mutant viral sequences, claims that are more analogous to those of the present application than the claims that were the subject of either *Amgen* or *Eli Lilly*, the Federal Circuit has clearly stated that "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met...even where actual reduction to practice of an invention is absent; and (3) *there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of a known structure.*" (emphasis added) 448 F.3d 1357, 1366, 79

U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006). See also, e.g., MPEP 2163(II)(A)(3)(a). As indicated in MPEP 2163(II)(A)(2), generally "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." Furthermore, in *Falkner v. Inglis,* the Federal Circuit held that "where...accessible literature sources clearly provided as of the relevant date, genes and their nucleotide sequences..., satisfaction of the written description requirement does not require either the recitation or incorporation by reference...of such genes and sequences." 448 F.3d 1357, 1368 (Fed. Cir. 2006).

Applicants contend that one of ordinary skill in the art would have readily recognized that Applicants were in possession of the invention as claimed in claims 20 and 21 and the dependent claims, including with respect to all mutant bacteria. In support, Applicants submit that (a) a variety of genes in a variety of different bacteria genuses had been identified at the time of filing that could serve as targets for attenuating mutations that would attenuate the ability of the bacteria to repair its modified nucleic acid (e.g., *uvrA* and *uvrB*), and (b) many of the nucleic acid targeted compounds that are taught in Applicants' specification for use in attenuating bacteria for proliferation are sequence independent, and therefore, species and genus independent.

Applicants' own specification provides a representative number of *uvrA* and *uvrB* mutants of different types of bacteria. Applicants' specification provides a working example of the attenuation of proliferation of *Escherichia coli uvrA* mutants in Figure 3 and Example 3 (paragraphs [0160]-[0161]. In addition, Applicants provide information regarding *uvrA*, *uvrB*, and/or *uvrC* genes, e.g., in paragraph [0120] at pages 56-57, in Example 9 (paragraphs [0190]-[0199] at pages 100-103, and in the working example of the attenuation of proliferation of *Bacillus anthracis* in Example 21 (paragraphs [0240]-[0249] at pages 129-133) of the specification.

In addition, *uvrA* and *uvrB* genes had been identified at the time of filing for a wide variety of bacteria. See, e.g., Aravind et al., Nucleic Acids Research 27(5):1223-1242 (1999), cited in

paragraph [0114] at page 52 of Applicants' specification, which states at page 1236, first column, third full paragraph, "The UvrABC excisionase, together with the UvrD helicase that is functionally coupled to it are the principal components of NER in bacteria (4) and are encoded in all bacterial genomes sequenced to date, including the minimal genomes of *Mycoplasma*." *UvrA* and *uvrB* genes that were known to those of ordinary skill in the art at the time of filing include, for example, *E. coli* (see, e.g., Husain, et al. The Journal of Biological Chemistry, 261:4895-4901 (1986); Arikan et al., Nucleic Acids Research, 14:2637-2650 (1986)), *Salmonella enterica serovar Typhi* (see, e.g., Genbank Acc. No. NC_004631), and *Shigella flexneri* (see, e.g., Genbank Acc. No. AE005674).

Also, one of ordinary skill in the art would have recognized that Applicants were in possession of the full scope of the claimed invention including for any type of bacteria, because the modification methods taught by Applicants for attenuating the bacteria for proliferation included (but were not limited to) methods that were largely or wholly sequence independent and therefore generally applicable to a wide variety of bacteria, regardless of the specific sequence of their DNA. For instance, one of ordinary skill in the art would readily recognize that knowledge about the specific genomic sequences of a particular bacteria are not relevant to the treatment of bacterial nucleic acid using certain nucleic acid targeted compounds such as a psoralen in combination with UVA irradiation. See, e.g., Lin (1998) Science and Medicine 5:2 11 (cited in paragraph [0296] of the specification) which discloses that a nucleic acid targeted compound, the psoralen S-59, reacts with and reduces the infectivity of a number of different types of bacteria.

2. *The application provides adequate written description to support the full scope of mutations claimed.*

The Examiner asserts in the Office Action mailed January 26, 2007 that the "specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the uvr gene's coding regions to target for modifications, in order to produce an attenuated bacterium." See page 15 of the Office Action. The Examiner further asserts that "one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutations (except, perhaps, deletion of the whole polynucleotide) that would result in a

decreased gene product activity." See pages 15-16 of the Office Action. The Examiner cites the reference, Bowie et al., in support of her assertions.

Applicants respectfully disagree with the Examiner's assertions and contend that the Bowie et al. reference does not support the Examiner's assertions. Furthermore, Applicants respectfully submit that the specification of the present application does provide a representative number of species regarding the types of mutations that is sufficient to support a genus claim. In light of the knowledge of those of skill in the art in this area, those of skill in the art would recognize from Applicants' specification that Applicants were, in fact, in possession of the full scope of the invention as claimed.

Applicants respectfully contend that, contrary to the assertions of the Examiner, the Bowie et al. reference is irrelevant to the present application. The Bowie et al. reference describes "how an analysis of allowed amino acid substitutions in proteins can be used to reduce the complexity of sequences and reveal important aspects of structure and function." See first paragraph on page 1306 of Bowie et al. The Examiner has pointed to nothing in the reference which would indicate that one of ordinary skill in the art would not readily envision multiple different ways that could be used to *disrupt* the expression or functionality of a given sequence. Even if it is true that one of ordinary skill in the art may often have trouble making amino acid substitutions in a particular protein sequence while still maintaining functionality, this is irrelevant to the present application. Unpredictability in making amino acid substitutions in a protein in which the structure-function relationship is unclear does not translate into there being unpredictability in the ability to *disrupt* the expression or function of a sequence. Regardless of how mysterious the structure-function relationships are, it would be obvious to one of ordinary skill in the art that disruption of expression and/or function of a gene would most likely occur if certain things are done, such as, but not limited to, any of the following: (a) deletion of the entire coding sequence; (b) deletion of the majority of the coding sequence; (c) generation of one or more stop codons early in the coding sequence; (d) a deletion early in the coding sequence that generates a frame-shift mutation (e) an insertion early in the coding sequence that generates a frame-shift mutation; (f) deletion of the promoter or other key control sequence; and (g) deletion of both the promoter and the coding sequence of the gene. The

effect of these types of mutations are far more predictable than the effect of the types of individual amino acid substitutions discussed in Bowie et al.

Furthermore, even if single point mutations in a gene are being made, one skilled in the art would recognize that such mutations would be more likely to disrupt the function of the gene than not. As noted above, with respect to point mutations, Griffiths et al. states that, "it is always true that such mutations are more likely to reduce or eliminate gene function (thus they are loss-of-function mutations) than to enhance it. The reason is simple: it is much easier to break a machine than to alter the way that it works by randomly changing or removing one of its components." (page 315; Griffiths, et al. (2002) Modern Genetic Analysis, W.H. Freeman and Co., New York, NY).

As indicated in MPEP 2163(II)(A)(2), generally "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." Applicants respectfully contend one of ordinary skill in the art would have been readily able to identify a wide variety of mutations for disrupting either expression of any target genes such as *uvrA* or *uvrB* and/or the functionality of the products of such genes and would have recognized Applicants as being in possession of such mutations. Since alternative methods for disrupting the expression or function of such genes would have been so obvious to one of ordinary skill in the art, it is not necessary to recite all such possible mutations or even any particular in order to meet the written description requirement. Applicants contend that, especially in light of the ease with which one of ordinary skill in the art could disrupt given target gene sequences in bacteria, the disclosures in the application are more than adequate to provide a representative number of species and meet the written description requirement for the full scope of the pending claims.

With respect to the modifications of the nucleic acid of the bacteria such that the bacteria are attenuated for proliferation, Applicants again contend that it would be apparent to one of ordinary skill in the art based upon Applicants' specification that Applicants were in possession of a

representative number of types of nucleic acid modifications generated using nucleic acid targeted compounds that react directly with the nucleic acid of bacteria such that the bacteria are attenuated for proliferation relative to the bacteria prior to modification. See, e.g., the extensive disclosure of a variety of exemplary nucleic acid targeted compounds in paragraphs [0098] – [0100] at pages 41-44 of Applicants' specification.

In light of above remarks, Applicants respectfully request that the rejection of claims 20-21, 83-87, 97-99, 100-105, 106, 107, 109-118, 128-130, 131-136, 137-138 and 139-149 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement be withrdrawn.

Claim Rejections under 35 U.S.C. § 102

1. Rejection of claims 20, 21, 83, 85, 86, 89, 96, 100, 110, 111, 112, 114, 116, 117, 127, 131 and 142 under Agrewala et al. (US 2002/0136738 A1).

Claims 20, 21, 83, 85, 86, 89, 96, 100, 110, 111, 112, 114, 116, 117, 127, 131 and 142 are rejected under 35 U.S.C. § 102(e) as being anticipated by Agrewala et al. (US 2002/0136738 A1).

Applicants respectfully traverse this rejection.

Claim 20 is directed to a method of preventing or treating a disease in a host, comprising administering to the host an effective amount of a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active. Dependent claims 83, 85, 86, 100, 110, 111, and 112 directly or indirectly depend from claim 20 and therefore incorporate all limitations of claim 20. Claim 21 is directed to a method of inducing an immune response in a host to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for

proliferation relative to the bacterium prior to modification, and wherein the modified bacterium expresses the antigen. Dependent claims 114, 116, 117, 127, 131, and 142 directly or indirectly depend from claim 21 and therefore incorporate all limitations of claim 21. Claims 89 and 96 are cancelled, without prejudice, by virtue of this Amendment and therefore the rejection with respect to these claims is considered moot.

To anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. Agrewala et al. fails to anticipate claims 20, 21, 83, 85, 86, 100, 110, 111, 112, 114, 116, 117, 127, 131 and 142, because the reference fails to teach or suggest each and every element of these claims. For example, Agrewala et al. does report administration of a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, *wherein gene expression in the modified bacterium is active* and/or *the modified bacterium expresses an antigen.*

On page 17 of the Office Action mailed January 26, 2007, the Examiner states regarding Agrewala et al., "In example 3, the Salmonella are grown in macrophages (antigen-presenting cells) which are attenuated by exposure to the alkylating agent mitomycin C and gamma radiation." Even if the treatment of infected cells with mitomycin C described in Example 3 would itself have been sufficient to attenuate the bacteria for proliferation, nothing in Example 3 or elsewhere in Agrewala et al. states that at the time the cells that had previously been treated with both mitomycin C and gamma irradiation were administered to an animal, gene expression was active in the Salmonella. Likewise, nothing in Example 3 or elsewhere in Agrewala et al. states that at the time the cells that had previously been treated with both mitomycin C and gamma irradiation were administered to an animal, expression of any antigen was active in the Salmonella in the previously treated cells.

On page 17 of the Office Action, the Examiner further states regarding Agrewala et al., "The reference also disclose [*sic*] that Mycobacterium tuberculosis is grown in macrophages and exposed to an agent (isonizid) [*sic*] acting on the nucleic acid." Even if isoniazid can act as a nucleic acid

targeted compound that reacts directly with bacterial nucleic acid, isoniazid is thought to kill *M. tuberculosis* primarily through a completely different mechanism, i.e., by targeting an enzyme called InhA in the bacteria. Thus, even if Agrewala et al. teaches the treatment of cells infected with *M. tuberculosis* with sufficient levels of isoniazid to attenuate the bacteria for proliferation, such a teaching still does not necessarily indicate that the bacteria are attenuated for proliferation due to the direct reaction of isoniazid with the nucleic acid of the bacteria. Furthermore, nowhere does Agrewala et al state that, at the time the infected cells that had previously been treated with both isoniazid and gamma irradiation are administered to an animal, gene expression or antigen expression is still active in *M. tuberculosis* in the infected macrophages.

Applicants further note that nowhere does Agrewala et al. state that maintaining expression of any genes in bacteria following treatment of macrophages infected with the bacteria with both drugs and gamma irradiation is necessary for the vaccines reported in the reference.

Since Agrewala et al. does not teach or suggest each and every element of claims 20, 21, 83, 85, 86, 100, 110, 111, 112, 114, 116, 117, 127, 131 and 142, Applicants respectfully request that the rejection of these claims under 35 USC § 102(e) be withdrawn.

2. Rejection of claims 20, 83, 85, 96, 97, 110, 111 and 112 under BASF AG (WO 89/09616).

Claims 20, 83, 85, 96, 97, 110, 111 and 112 are rejected under 35 U.S.C. § 102(b) as being anticipated by BASF AG (WO 89/09616).

Applicants respectfully traverse this rejection.

Claims 20, 83, 85, 110, 111 and 112 are as described above. Claim 97 is a dependent claim of claim 20, and therefore incorporates all limitations of claim 20, described above. Claim 96 is cancelled, without prejudice, by virtue of this Amendment and therefore the rejection with respect to this claim is considered moot.

As noted above, to anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. BASF AG fails to anticipate claims 83, 85, 97, 110, 111 and 112, because the reference fails to teach or suggest each and every element of these claims. For example, BASF AG does not provide a description of a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification.

Although the Examiner has stated that the reference "discloses Vibrio anguillarium strains which are attenuated by alkylating agents (mitomycin C, methylmethane sulfonate; pages 4-5) and which are used as a vaccine" (page 17 of Office Action mailed January 26, 2007), Applicants respectfully disagree. The passage of BASF AG to which the Examiner appears to be referring actually merely states at line 30 of page 4 to line 2 of page 5 as follows:

> In the present context, the term "mutant strain" is defined as a strain which has been isolated as a spontaneous mutant (a frequent phenomenon in nature) or in which a mutation has been deliberately induced by subjecting a parent bacterial strain to treatment with a mutagen such as ultraviolet radiation, ionizing radiation, or a chemical mutagen such as mitomycin C, 5-bromouracil, methylmethane sulphonate, nitrogen mustard, or a nitrofuran, or by applying recombinant DNA techniques.

In the cited passage, alternative methods by which a mutant strain may be produced are presented. Mitomycin C and methylmethane sulfonate are each referred to as a "chemical mutagen" used to induce a mutation in a "*parent* bacterial strain" (emphasis added). Nowhere does either this passage or the rest of the reference state that a bacterium that is *itself* reacted with the mitomycin C or methylmethane sulfonate is a bacterium that can or should be used in a vaccine. Even *if* BASF AG taught that the mutant progeny of such a bacterium reacted with the mitomycin C or methylmethane sulfonate were to be used in a vaccine, the reference would still fail to teach a "vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a

nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification."

Since BASF AG does not teach or suggest each and every element of claims 20, 83, 85, 97, 110, 111 and 112, Applicants respectfully request that the rejection of claims 20, 83, 85, 97, 110, 111 and 112 under 35 USC § 102(b) be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claims 20, 21, 83, 84, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 119, 120-130, 136, 140-142 and 145 are rejected under 35 U.S.C. § 103(a) as being unpatentable over AKZO (WO 02/40046) in view of Sander et al. (Infect. Immun. June 2001 69(6): 3562-3568) and Ferguson et al. (Mutation Research. 1987. 184: 13-21).

Applicants respectfully traverse this rejection.

Claims 20-21 are as described above. Claims 83-84 and 97-112 depend directly or indirectly from claim 20 and therefore incorporate all limitations of claim 20. Claims 114-117 and 128-130, 136, 140-142, and 145 depend directly or indirectly from claim 21 and therefore incorporate all limitations of claim 21. Since claims 88-96 and claims 119-127 are cancelled, without prejudice, by virtue of this response, the rejection of these claims is considered moot.

To establish a prima facie case of obviousness, the cited prior art references, alone or in combination, must teach or suggest each and every claim limitation. Applicants respectfully submit that claims 20, 21, 83, 84, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 128-130, 136, 140-142 and 145 are not obvious over AKZO, in view of Sander et al. and Ferguson et al., because the references do not teach or suggest each and every element of the claims. For example, none of these references, alone or in combination, describes a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, *wherein gene expression in the modified bacterium is active* or *the modified bacterium expresses an antigen.* None of the cited references,

alone or in combination, teach that after treatment with a nucleic acid targeted compound, bacteria, with or without a mutation in a gene such as *recA*, *uvrA*, or *uvrB*, would or could still express genes.

Applicants further submit that one of ordinary skill in the art would not have been motivated to combine the teachings of the cited references. For instance, one of ordinary skill in the art would not have been motivated to combine the teachings of AKZO and Sander et al. (even in light of Ferguson et al.) to produce the compositions or methods of the rejected claims. AKZO states that *live* attenuated Salmonella strains are suitable for vaccines. See, e.g., Abstract of AKZO. Even if Sander et al. shows that "a recA deletion mutant of Mycobacteria bovis has an increased susceptibility to DNA-damaging agents" as stated by the Examiner (page 19 of Office Action mailed January 26, 2007), this does not teach that treatment of a *recA* mutant bacterium with a DNA-damaging agent would generate a bacterium that was suitable as a vaccine. In fact, Sander et al. teaches away from such a combination when the references states, e.g., "The results indicate that RecA does not contribute to the establishment and maintenance of infection. This is an important finding since persistence of BCG following vaccination is thought to be a significant contributory factor to its immunogenicity; a mutant BCG which is rapidly eliminated is unlikely to be an effective vaccine." See lines 8-13 of second column of page 3567. To the degree that Sander et al. reports that survivability/viability of the *recA* deletion mutants that had been treated with the DNA-damaging reagents was significantly reduced (see, e.g., Figure 3 and Figure 5 of Sander et al.), Sander et al. would have suggested to one of ordinary skill in the art that even if *recA* deletion mutants are suitable for use in a live vaccine, treating those mutants with DNA-damaging agents *prior* to using them as vaccines would not be desirable, since the immunogenicity of the bacteria would have been expected to be reduced. Applicants respectfully submit that to think otherwise constitutes impermissible hindsight based on Applicants'own teachings.

Lastly, Applicants note that the Examiner has stated, "Additionally, as uvrA, uvrB are well known in the prior art as enzymes responsible for DNA repair, see Ferguson et al, they represent an obvious functional alternative for recA." See page 19 of the Office Action mailed January 26, 2007. Applicants submit that if the Examiner is really of the opinion that the known enzymes responsible for DNA repair are obvious functional alternatives of each other, then the Examiner should be

examining each of the species *phr*B, *uvr*A, *uvr*B, *uvr*C, *uvr*D and/or *rec*A that are recited in the claims, without requiring a species election to only *uvrA* and *uvrB*.

Since AKZO, Sander et al. and Ferguson et al. do not teach, either alone, or in combination, all elements of claims 20, 21, 83, 84, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 128-130, 136, 140-142 and 145, and further, the references themselves teach away from such a combination, Applicants respectfully request that the rejection of these claims under 35 USC § 103 be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 282172002800. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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